Remarks

Claims 34-40 and 48-49 are pending in this application. No claim amendments are made in this paper. Applicants respectfully submit that all of the pending claims are allowable for the following reasons.

A. The Rejections Under 35 U.S.C. § 112, ¶ 2, Should Be Withdrawn

On page 2 of the Office Action, claims 35, 36, 37, 48 and 49 are rejected under 35 U.S.C. § 112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter of the invention. Applicants respectfully traverse these rejections.

First, it is alleged that claims 35, 37 and 48 are indefinite because these claims do not recite "further procedural steps." Office Action, page 2. Applicants respectfully submit that there is no requirement that dependent method claims recite "further procedural steps." Indeed, "a claim that makes reference to a preceding claim to define a limitation is an acceptable claims construction [unless] ... where the format of making reference to limitations recited in another claim results in confusion." *Manual of Patent Examining Procedure* ("MPEP"), § 2173.05 (f). Such is not the case here, and the Examiner has not alleged that the claims result in any confusion. Consequently, claims 35, 37 and 48 satisfy the requirements of 35 U.S.C. § 112, ¶ 2.

Second, claim 37 is rejected because it allegedly fails to identify the particular drugs for which avoidance of interaction is intended. Office Action, page 2. Applicants respectfully submit that, although names of particular drugs are not recited by claim 37, the claim is sufficiently particular as to what drugs for which avoidance of interaction is intended. It is well-known what drugs inhibit cytochrome P450. *See, e.g.*, Harrison's Principles of Internal Medicine, 13th Ed., p.p. 402-403 (1994), a copy of which is attached hereto as **Exhibit A**, wherein phrases such as "other of the known inhibitors of P450 3A" are used without further explanation, as well as various examples of cytochrome P450 inhibiting agents are given.

Indeed, the interaction between pharmaceuticals that inhibit cytochrome P450 has been a concern in the pharmaceutical industry. *See, e.g.*, Simons *et al.*, *The New Eng. J. Med.*, 330(23): 1663-1670 (1994) at page 1667, a copy of which is attached hereto as **Exhibit B**. Moreover, examples of "a drug that inhibits cytochrome P450" are clearly disclosed, for example, in page 11, lines 27-29 of the

specification. Consequently, because "[t]here is nothing inherently wrong with defining some part of an invention in functional terms," Applicants respectfully submit that the rejection of claim 37 be withdrawn. MPEP, § 2173.05 (g).

Third, the rejection of claim 36 as allegedly indefinite should also be withdrawn, since the "[b]readth of a claim is not equated with indefiniteness." MPEP § 2173.04, citing *In re Miller*, 441 F.2d 689, 693 (C.C.P.A. 1971). Accordingly, "[i]f the scope of the subject matter embraced by the claims is clear, and if applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims, *then the claims comply with 35 U.S.C. 112, second paragraph*." *Id.* (emphasis added).

Applicants respectfully point out that the term "cancer," although it may have a number of sub-types, is a well-defined term known to those of ordinary skill in the art. In addition, Applicants "have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims." *Id.* Therefore, Applicants respectfully request that the rejection of claim 36 be withdrawn.

Fourth, the rejection of claims 36 and 49 as allegedly indefinite should also be withdrawn. Here, it is alleged that the claims are "incomplete for failure to specify the step or steps to be taken to determine the particular hosts." Office Action, page 2. Presumably, the Examiner is referring to the phrase "human [who] has a higher than normal propensity for cancer," as recited by claim 36. However, such patients are readily identifiable by those of ordinary skill in the art. As evidenced by The Merck Manual, 16th Ed., p.p. 1263-1264 (1992), a copy of which is attached hereto as **Exhibit C**, various risk factors for cancer are known in the art. Such factors include age, environmental factors, and family history of cancer. Therefore, individuals with higher risk factors can be readily identified based on their family history, area of work and residence, and/or medical screenings. Identification of a patient with higher propensity for developing cancer is in fact routinely practiced in the medical art. Therefore, Applicants respectfully request that the rejection of claims 36 and 49 be withdrawn.

B. The Rejections Under 35 U.S.C. § 112, ¶ 1, Should Be Withdrawn

On pages 2-3 of the Office Action, claims 35, 36, 37, 48 and 49 are rejected under 35 U.S.C. § 112, ¶1, as allegedly lacking written description support.

First, it is alleged that claims 35 and 48 "failed to overcome the description" of U.S. Patent No. 4,659,716 to Villani *et al.* ("Villani") that "DCL and the fluoro analogue thereof do not generate CNS side effects and are also non-sedating."[1] Office Action, page 2. It is further alleged that because Bocian reference, cited in the Office Action, indicates that "loratadine has an excellent safety records," clams 35 and 48 lack adequate support.[2] Applicants respectfully traverse this rejection.

Claims 35 recites, in part, a method comprising reducing or avoiding adverse effects *associated with non-sedating antihistamines*. Contrary to the Examiner's allegation, Villani does not teach that the compounds it discloses can be used while reducing or avoiding adverse effects *associated with non-sedating antihistamines*. This is because Villani's disclosure of compounds allegedly having reduced CNS-adverse effects cannot be interpreted to mean that the compounds have less adverse effects than other non-sedating antihistamines, since *an antihistaminic agent is deemed to be non-sedating precisely because it has reduced CNS side-effects*. *See* Villani, col. 10, lines 38-40 ("the compounds of the invention are a potent antihistamines having low CNS activity *indicative* of non-sedation." (emphasis added)). Therefore, Villani, by disclosing that the compounds have reduced side-effects, teaches nothing more than the proposition that those compounds are non-sedating. Villani discloses nothing with regard to those compounds' ability to reduce or avoid *adverse effects associated with other non-sedating antihistamines*.

Furthermore, Bocian's statement that loratadine has an excellent safety record adds nothing to the substance of the rejection. This is because the proposition that loratadine has an excellent safety record, even if true, is simply irrelevant to whether or not DCL would reduce or avoid the adverse effects associated with other non-sedating antihistamines. Therefore, Applicants respectfully request that the rejection of claims 35 and 48 be withdrawn.

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[1] It is unclear as to why the claims must "overcome" the cited references in order to satisfy the written description requirement.

[2] This assertion seems to imply that example 5 is not convincing because tit compares DCL and terfenadine, not DCL and loratadine. However, such an implication is non-sensical. The claims at issue recite, in part, "reducing or avoiding adverse-effects associated with *non-sedating antihistamines*," of which *terfenadine* is a member. Applicants do not understand why a comparison between DCL and loratadine is required in order for the claims to have adequate written description support.

Second, claims 36 and 49 are rejected because example 4 of the specification allegedly fails to provide a "convincing factual basis for ... [the] conclusion ... that 'DCL is 5-7 fold less active than loratadine at promoting tumor growth'." Office Action, page 3. This is allegedly because "there is no apparent prior art basis *within the disclosure*" that provides an explanation or rationale for Applicants' conclusion. *Id.* (emphasis added). Applicants respectfully disagree.

It is well-settled that the standard for determining compliance with the written description requirement is whether "the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." MPEP § 2163.02, citing *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989). Therefore, as long as the description is clear to persons of ordinary skill in the art, no "apparent prior art basis *within the disclosure*" that explains the rationale of conclusion made in the description is necessary. Applicants respectfully submit that the specification, in particular example 4, is sufficiently clear so as to allow those of ordinary skill in the art to recognize that the conclusion reached by Applicants is properly founded on the experimental results provided therein.

Example 4 clearly states that "[i]nhibition of lymphocyte mitogenesis was used to screen the potencies of loratadine and DCL as tumor promoting agents." Specification, page 23, lines 33-35. As evidenced by Brandes *et al.*, *J. Natl. Cancer Institute*, 86(10): 770-775 (1994) ("Brandes"), the abstract of which is attached hereto as **Exhibit D**, testing a compound for its ability to inhibit lymphocyte mitogenesis was an well-accepted procedure to assess the compound's potency in promoting tumor growth at the time of this invention. Brandes discloses testing of five antihistamines for their potencies to promote tumor growth. Brandes, Abstract. One of the procedures used was inhibition of lymphocyte mitogenesis. *Id.* From its results, Brandes concludes that the assays, including inhibition of lymphocyte mitogenesis, properly predicted the propensity of the tested compounds' propensity to stimulate cancer growth. *Id.* Therefore, the inhibition of lymphocyte mitogenesis was a well-accepted procedure for the assessment of a compound's propensity to promote tumor growth at the time of this invention. Thus, Applicants respectfully request that the rejection of claims 36 and 49 be withdrawn.

Third, it is alleged in the Office Action that claim 37 is not adequately supported by the written description because example 6 is entirely prospective,

allegedly rendering claim 37 lacking in factual support. Applicants respectfully traverse this rejection.

Again, the standard is whether "the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." MPEP § 2163.02. Furthermore, "[a] description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption." *Id.* at § 2163.04. The Examiner, therefore, "has the initial burden of presenting by a preponderance of evidence *why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims.*" *Id.* (emphasis added).

Claim 37 recites, in part, avoiding an interaction between DCL and a drug that inhibits cytochrome P450. Such an embodiment is literally repeated several times in the specification. *See, e.g.*, specification, page 7, lines 16-24. As such, it cannot be clearer that claim 37 recites what was invented, and those of ordinary skill in the art would have recognized that fact.

Furthermore, the Examiner's allegation that claim 37 lacks adequate written description support because example 6 is prospective is completely unfounded. This is because "[s]imulated or predicted test results and prophetical examples ... are permitted in patent applications." MPEP § 608.01(p), II. Therefore, Applicants respectfully submit the rejection, based on an allegation that claim 37 lacks adequate support simply because example 6 is prophetic, cannot be maintained.

Finally, the Examiner fails to provide any evidence or reasoning as to "why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims." MPEP § 2163.04. All that is provided is an unfounded allegation that claim 37 lacks an adequate written description support because example 6 is prospective. As such, Applicants respectfully submit that the Examiner did not overcome his initial burden of establishing a *prima facie* case of lack of written description.

For at least the foregoing reasons, Applicants respectfully request that the rejection of claim 37 also be withdrawn.

C. The Rejection Under 35 U.S.C. § 103(a) Should Be Withdrawn

On pages 3-4 of the Office Action, claims 34-40 and 48-49 are rejected as allegedly obvious over Berkow *et al.*, *The Merck Manual of Diagnosis and*

Therapy, 16th Ed., pp 332-334 (1992) ("Berkow") in view of Villani. In particular, it is alleged that because Berkow discloses that symptoms of urticaria can be relieved with an antihistamine, and Villani discloses DCL and related compounds are antihistamines with low CNS-related side effects, *i.e.*, non-sedative, the claims are obvious.[3] Applicants respectfully traverse this rejection.

As the Examiner is well aware, three basic criteria must be met to establish a case of *prima facie* obviousness: first, there must have been at the time of the invention a motivation to combine the references cited; second, the alleged prior art must teach or suggest all of the limitations of the claims alleged to be obvious; and third , there must have been at the time of the invention a reasonable expectation of success. MPEP § 2142. In addition, a *prima facie* case of obviousness may be rebutted by showing that the claimed invention achieves unexpected results or by showing that the art teaches away from the claimed range. MPEP § 2144.05(III).

The pending claims recite, in part, a method of treating urticaria in a human in need thereof, which comprises administering a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof. Applicants respectfully submit that the cited art does not disclose or suggest the claimed invention, much less provide the legally required reasonable expectation of success.

The primary reference, Berkow, discloses that symptoms of acute urticaria *usually can* be relieved with oral *first generation* anti-histamines, such as diphenhydramine, hydroxyzine, or cyprohependine. *See* Berkow, Page 333. However, Berkow does not disclose or suggest the use of any second generation non-sedating antihistamines, much less DCL, to treat urticaria. In addition, hydroxyzine (one of the agents Berkow suggests to treat urticaria) has been reported to *induce* urticaria rather than treat it. *See* Michel *et al.*, Skin Reactions to Hydroxyzine, *Contact Dermatitis*, **1997**, *36*, 147-149 ("Michel"), a copy of which was submitted with Applicants' response of April 23, 2001, the entirety of which is incorporated herein by reference. Therefore, Michel, at the very least, imparted confusion in the art, if it did not completely refute Berkow's suggested use of hydroxyzine against urticaria.

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[3] Applicants note that the rejection is based, in part, on "the teaching by applicant that DCL has the expected effect in the treatment of urticaria." Office Action, page 4. However, Applicants' own disclosure cannot form a basis for rejecting claims under 35 U.S.C. § 103. *See In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991).

More importantly, it has been shown that certain types of urticaria do not respond at all to antihistaminic drugs. *See* Parslew *et al.*, Warfarin Treatment of Chronic Idiopathic Urticaria and Angio-Oedema, *Clinical and Experimental Allergy*, **2000**, *30*, 1161-1165, a copy of which was submitted with Applicants' response of April 23, 2001. Such art is directly contrary to Berkow and must be considered by the Examiner. MPEP § 2141 (citing *Graham v. John Deere Co.*, 383 U.S. 1 (1966)). When proper consideration is given to the art as a whole, it is clear that the contention that Berkow suggests that DCL can be expected to treat urticaria is meritless.

Villani does not remedy the deficiencies of Berkow. Villani discloses a class of compounds of the type: 7- or 8-(halo)-substituted-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta-[1,2-b]pyridines. *See* Col. 1, lines 17-38. Although Villani alleges this class of compounds can be shown to have antihistaminic activity, Villani does not disclose or even suggest the treatment of urticaria with any of its compounds, much less treating urticaria with DCL.

Therefore, Berkow merely suggests treating the symptoms of urticaria with a first generation sedating antihistamine, and Villani only discloses treating allergic reactions using second generation antihistamines and says nothing about urticaria. Further, neither reference alone or in combination discloses or suggests a method of treating urticaria, while reducing or avoiding adverse effects associated with non-sedating antihistamines.

In addition, as the Examiner is aware, in order to form a proper basis for a rejection under 35 U.S.C. § 103, the prior art must provide some suggestion, either explicit or implicit, of the combination that allegedly renders a claimed invention obvious. MPEP § 2142. This suggestion is absent from the cited references. This is because the disclosure of Berkow and Villani are directed to different classes of compounds and different indications. Thus, those of ordinary skill in the art would not have been motivated to combine these two references.

Furthermore, Applicants respectfully submit that unexpected results have also been demonstrated in the specification as filed, contrary to the Examiner's allegation.[4] Applicants respectfully direct the Examiner's attention to the Examples

[4] In this regard, Applicants by no means concede that a *prima facie* obviousness has been established. Quite to the contrary, Applicants believe that a *prima facie* obviousness has NOT been established, and the consideration of unexpected results is not even necessary.

section of the specification. The Examples describe the therapeutic activity of DCL, while avoiding or reducing adverse effects associated with other second generation antihistamines. This is particularly important in view of the fact that at the time prior to the claimed invention, compounds of the class of non-sedating antihistamines (*e.g.*, loratadine, terfenadine, astemizole) were known to cause or have a potential for causing severe adverse effects, such as ventricular fibrillation, cardiac arrhythmias, and tumor growth. This application describes a variety of surprising and unexpected benefits conferred by the claimed invention. For example, example 4 illustrates that DCL is 5-7 fold less active than loratadine at promoting tumor growth. *See* Specification at Page 24. Example 5 demonstrates that DCL is less active than terfenadine in inhibiting the cardiac delayed rectifier and thus has reduced potential for cardiac side-effects. *See* Specification at Pages 24-26. Such results are evidence of unexpected results that can rebut even a *prima facie* case of obviousness.

In sum, Applicants submit that: 1) a *prima facie* case of obviousness has not been established by the combination of Berkow and Villani; and 2) even assuming that a *prima facie* case of obviousness has been established, the claims are not obvious because unexpected results are properly shown in this application. Therefore, Applicants respectfully request that the rejection of claims 34-40 and 48-49 be withdrawn.

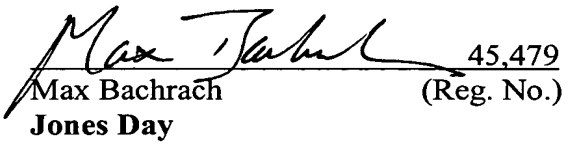
Conclusion

Applicants respectfully submit that all of the pending claims are allowable, and request that rejections directed to the claims be withdrawn.

No fee is believed due for this submission. Should any additional fees be due for this submission or to avoid abandonment of the application, please charge such fees to Jones Day Deposit Account No. 503013.

Respectfully submitted,

Date August 20, 2004



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